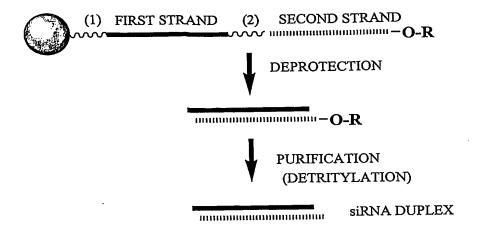
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Figure 1

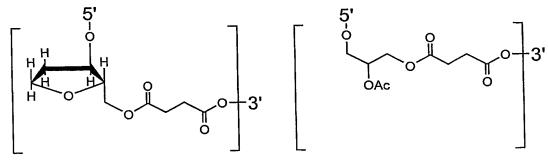


= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP FOR EXAMPLE: DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

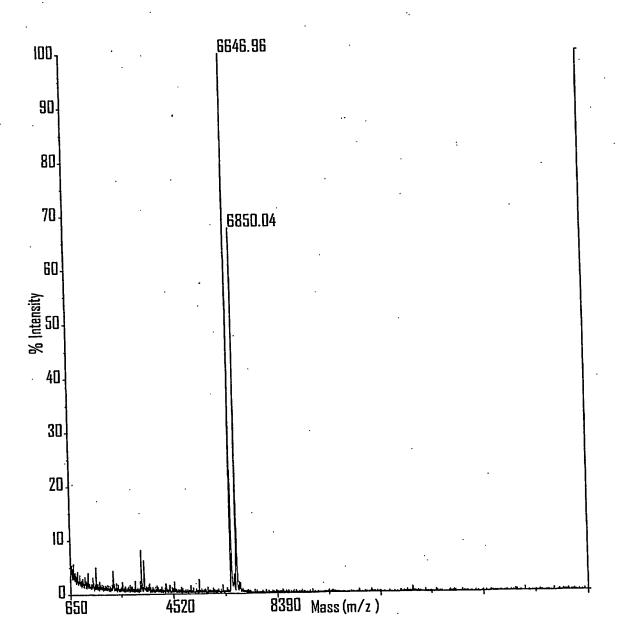
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

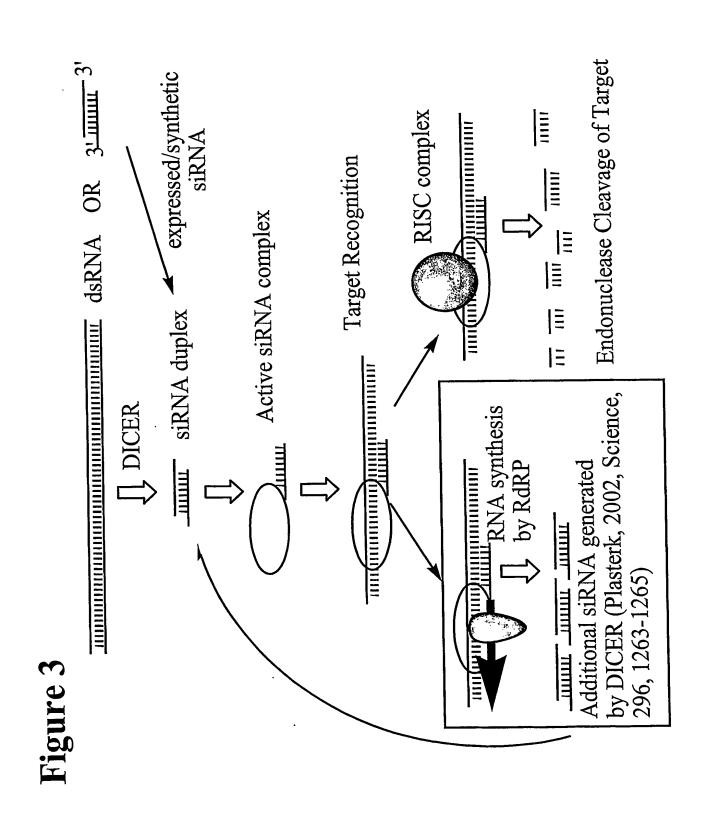


INVERTED DEOXYABASIC SUCCINATE LINKAGE

GLYCERYL SUCCINATE LINKAGE

Figure 2





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Figure 4 SENSE STRAND (SEQ ID NO 1883) ALL POSITIONS RIBONUCLEOTIDE EXCEPT PÓSITIONS (N N) 5'--3' -5' 3'-ANTISENSE STRAND (SEQ ID NO 1884) ALL POSITIONS RIBONUCLEOTIDE EXCEPT POSITIONS (N N) SENSE STRAND (SEO ID NO 1885) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-OM EXCEPT POSITIONS (N N) 5'--3' В -51 3'-ANTISENSE STRAND (SEO ID NO 1886) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1887) ALL PYRIMIDINES = 2'-O-ME OR 2'-FLUORO EXCEPT POSITIONS (N N) 5'--3' -51 3'-ANTISENSE STRAND (SEQ ID NO 1888) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) SENSE STRAND (SEO ID NO 1889) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY 5'--3 L-(N_sN) NNNNNNNNNNNNNNNNNNNN -5' 3'-ANTISENSE STRAND (SEQ ID NO 1886) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1890) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) 5'--3' \mathbf{E} -5' ANTISENSE STRAND (SEQ ID NO 1886) ALL PYRIMIDINES = 2'-FLUORO AND ALL PURINES = 2'-O-ME EXCEPT POSITIONS (N N) SENSE STRAND (SEQ ID NO 1889) LL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY 5'--3' ${f F}$ 3'--51 ANTISENSE STRAND (SEQ ID NO 1891) ALL PYRIMIDINES = 2'-FLUORO EXCEPT POSITIONS (N N) AND ALL PURINES = 2'-DEOXY

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES

B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT

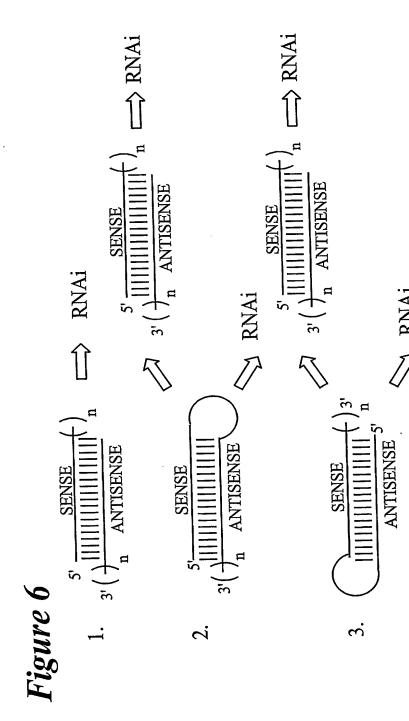
L = GLYCERYL OR B THAT IS OPTIONALLY PRESENT

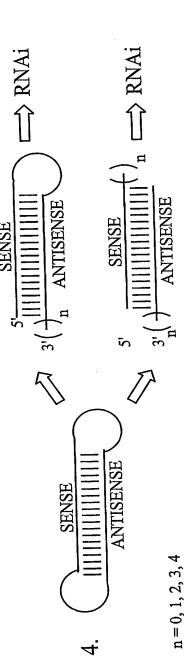
S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE THAT IS OPTIONALLY ABSENT

Figure 5 SENSE STRAND (SEQ ID NO 1892) iB-CAUGGCUGCCAUCUGCGCC*TT*-iB -31 L-T_ST GUACCGACGGUAGACGCGG -5' 3'-ANTISENSE STRAND (SEQ ID NO 1893) SENSE STRAND (SEQ ID NO 1894) -3' $c \underline{\mathbf{a}} \underline{\mathbf{u}} \mathbf{g} \mathbf{g} \underline{\mathbf{c}} \underline{\mathbf{u}} \mathbf{g} \underline{\mathbf{c}} \underline{\mathbf{c}} \underline{\mathbf{a}} \underline{\mathbf{u}} \underline{\mathbf{c}} \underline{\mathbf{u}} \mathbf{g} \underline{\mathbf{c}} \mathbf{g} \underline{\mathbf{c}} \underline{\mathbf{c}} T_{\mathbf{S}} T$ 5'-B -5' $L-T_ST$ gu \underline{a} c c \underline{g} \underline{a} c \underline{g} \underline{g} u \underline{a} \underline{g} \underline{a} c \underline{g} \underline{c} \underline{g} \underline{g} 3'-ANTISENSE STRAND (SEQ ID NO 1895) SENSE STRAND (SEQ ID NO 1896) -3' iB-cAuGGcuGccAucuGcGccTT-iB 5'-L-T_ST G u A c c G A c G G u A G A c G c G G -5' 3'-ANTISENSE STRAND (SEQ ID NO 1897) SENSE STRAND (SEQ ID NO 1898) iB-cAuGGcuGccAucuGcGccTT-iB -31 5'-D -5' $L-T_ST$ gu a c c g a c g g u a g a c g c g g 3'-ANTISENSE STRAND (SEQ ID NO 1895) SENSE STRAND (SEQ ID NO 1899) iB-cAuGGcuGccAucuGcGcc TT-iB 5'--3' E -5' $L-T_STgu\underline{a}cc\underline{g}\underline{a}c\underline{g}gu\underline{a}\underline{g}\underline{a}c\underline{g}c\underline{g}g$ 3'-ANTISENSE STRAND (SEQ ID NO 1895) SENSE STRAND (SEQ ID NO 1898) iB-cAuGGcuGccAucuGcGccTT-iB -3' 5'-F L-T_ST Gu A c c G A c G G u A G A c G c G G -5' 3'-ANTISENSE STRAND (SEQ ID NO 1900)

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro
italic lower case = 2'-deoxy-2'-fluoro
underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXY
iB = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY OR iB OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR
PHOSPHORODITHIOATE OPTIONALLY PRESENT





<u>.</u> .

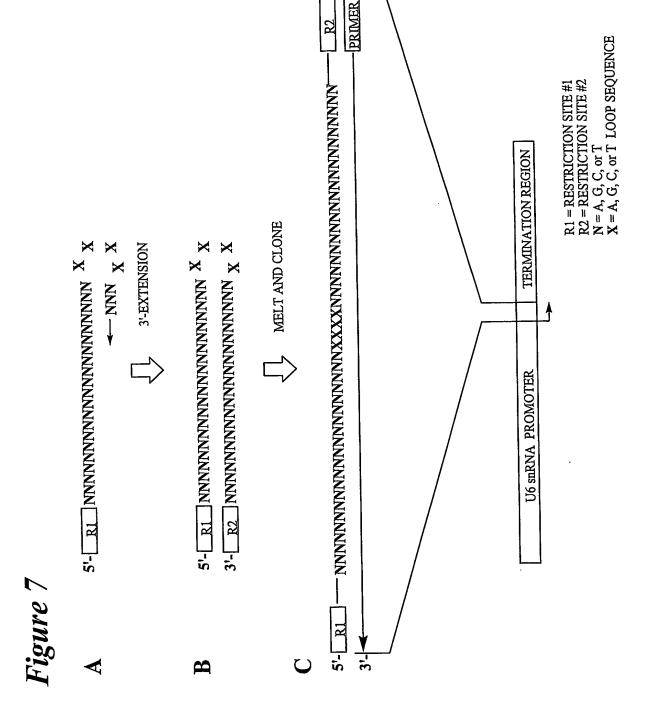


Figure 8

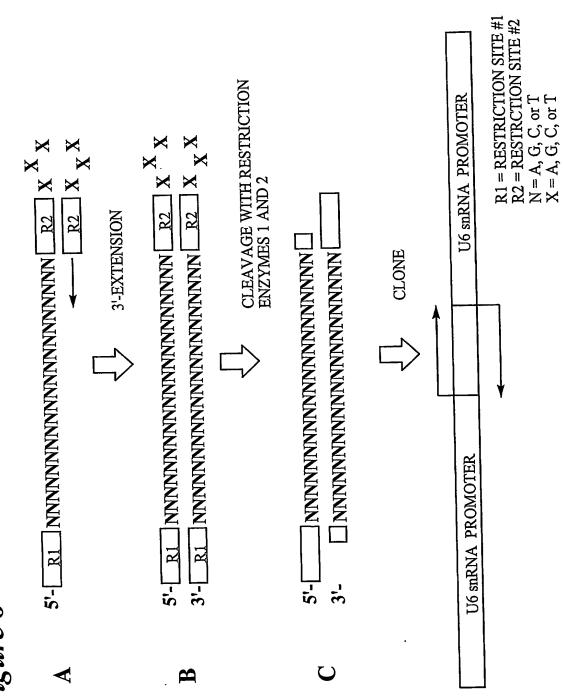
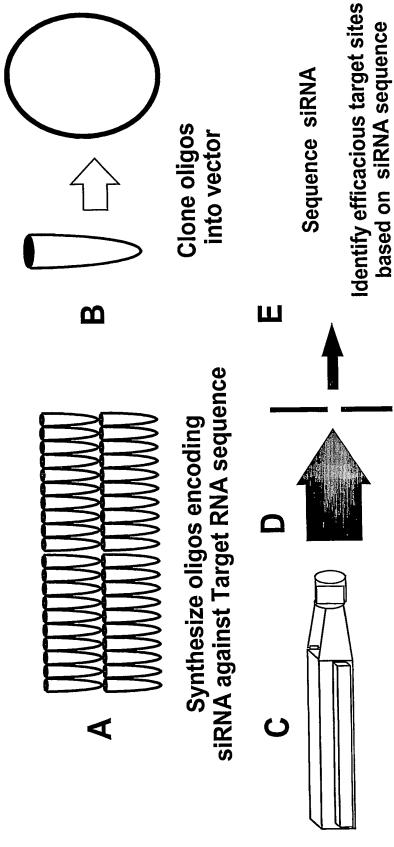
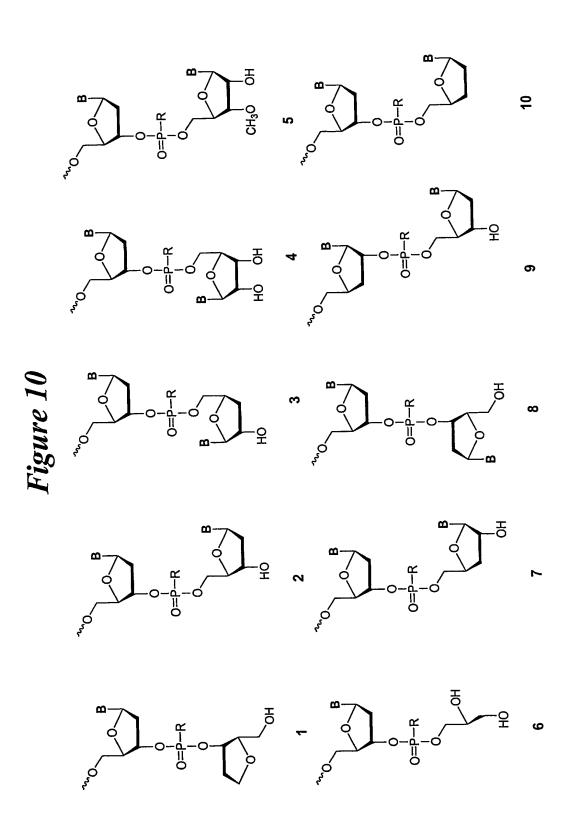


Figure 9: Target site Selection using siRNA



Select cells exhibiting desired phenotype

Transduce target cells



R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy

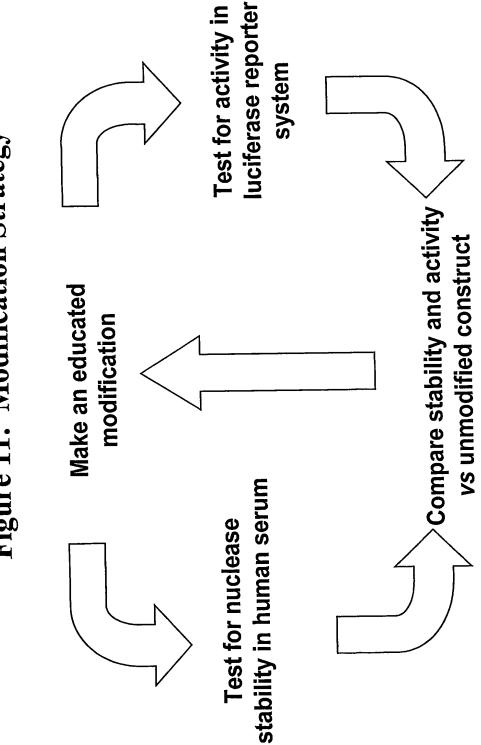
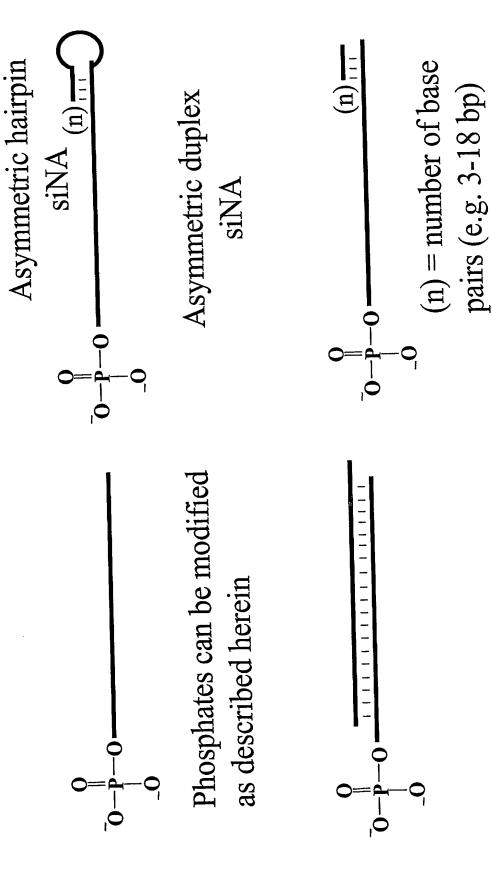


Figure 12: Phosphorylated siNA constructs



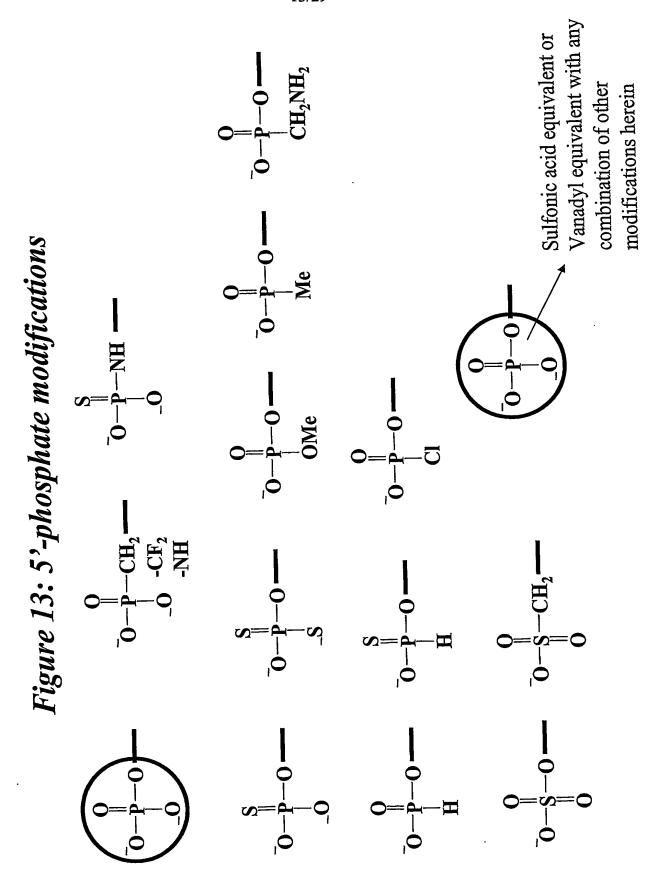


Figure 14A: Duplex forming oligonucleotide constructs that utilize Palindrome or repeat sequences

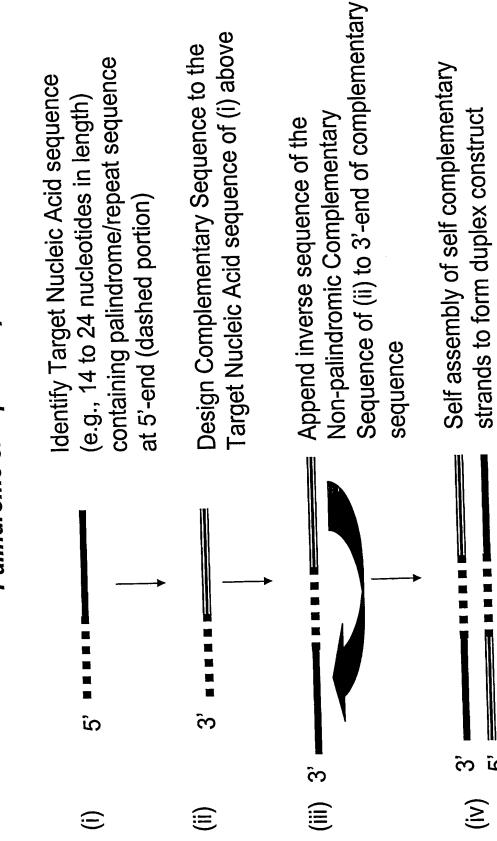


Figure 14B: Example of a duplex forming oligonucleotide sequence

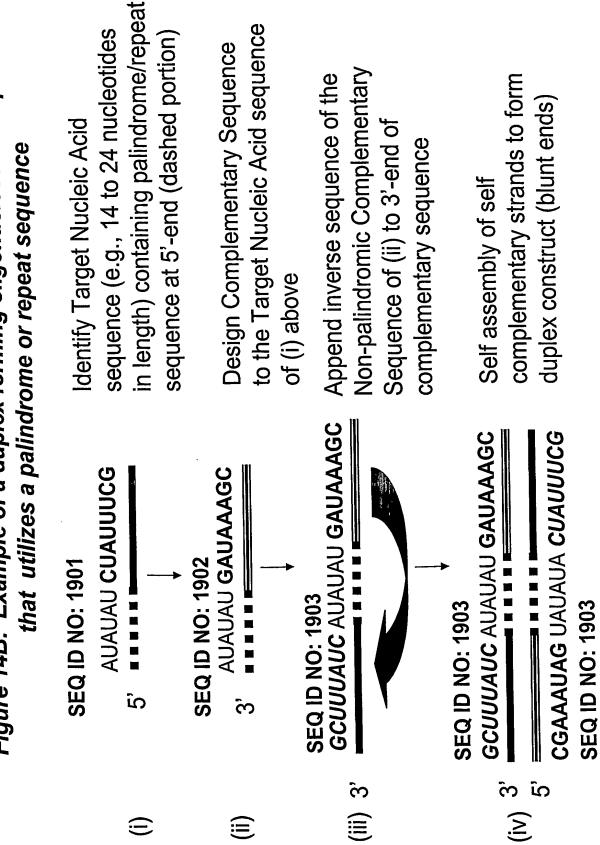


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

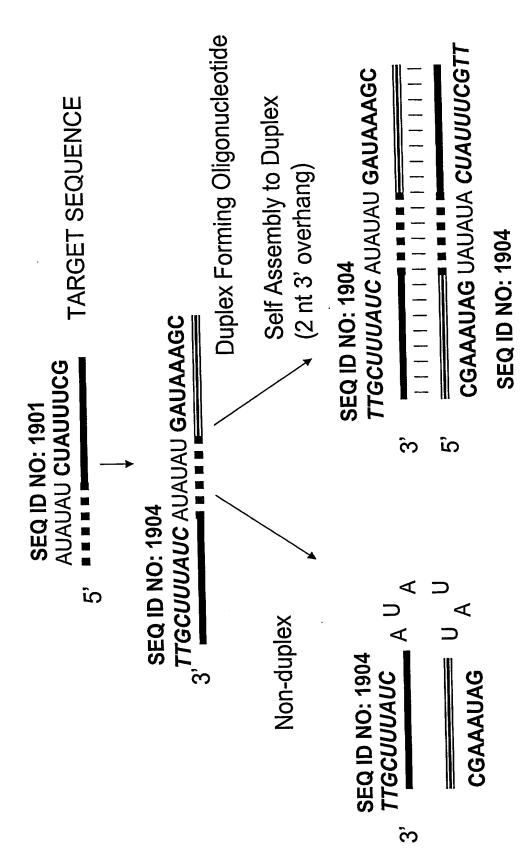


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition

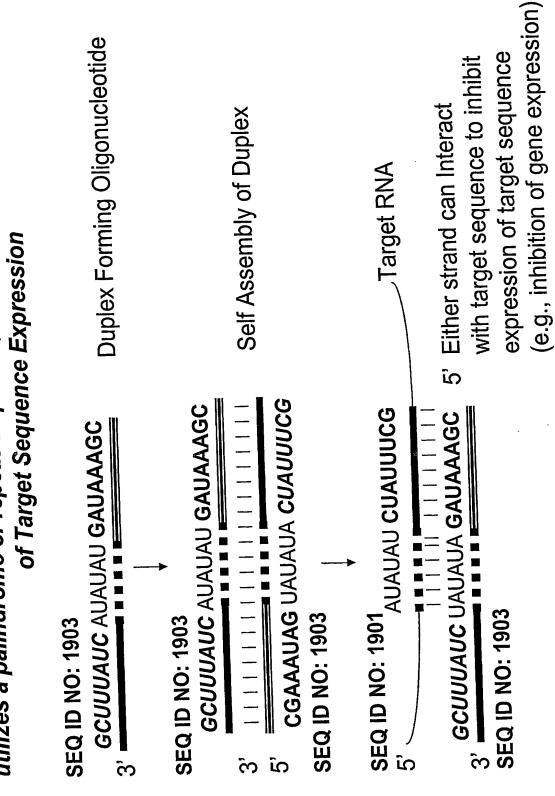


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences

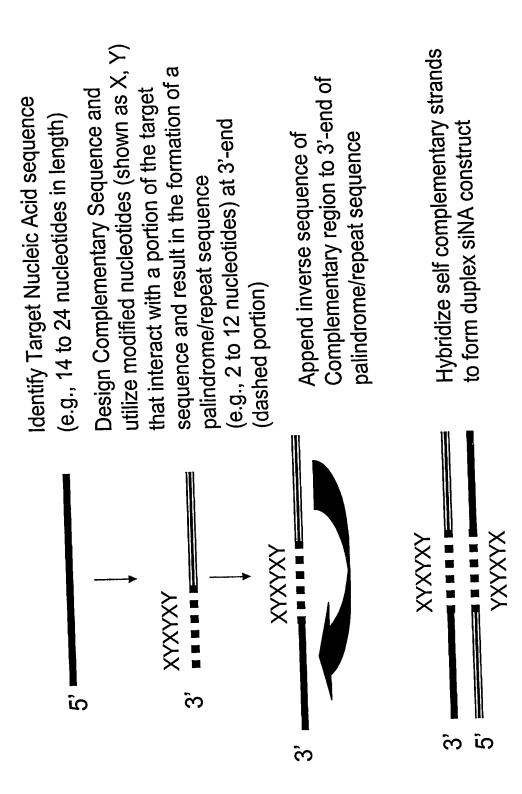
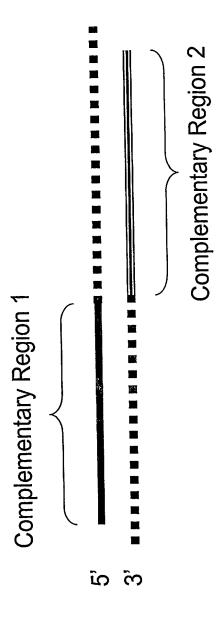


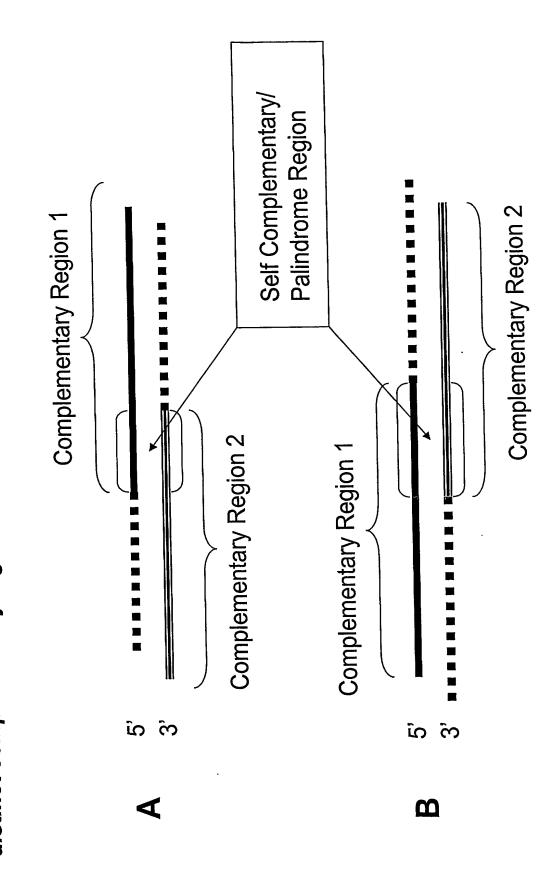
Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions Complementary Region 1 Complementary Region 2 က် က်



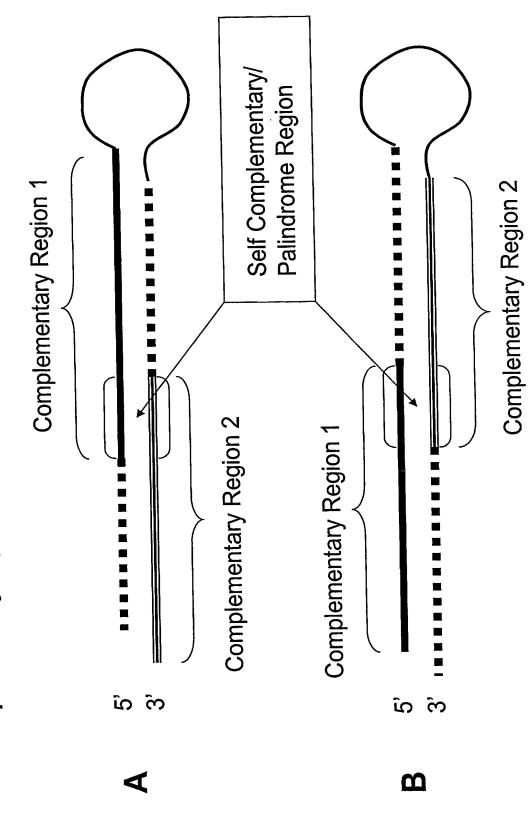
 $\mathbf{\omega}$

Figure 17: Examples of hairpin multifunctional siNA constructs Complementary Region 1 Complementary Region 2 with distinct complementary regions Complementary Region 2 Complementary Region 1 က်က် က် က် $\mathbf{\omega}$ 4

Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

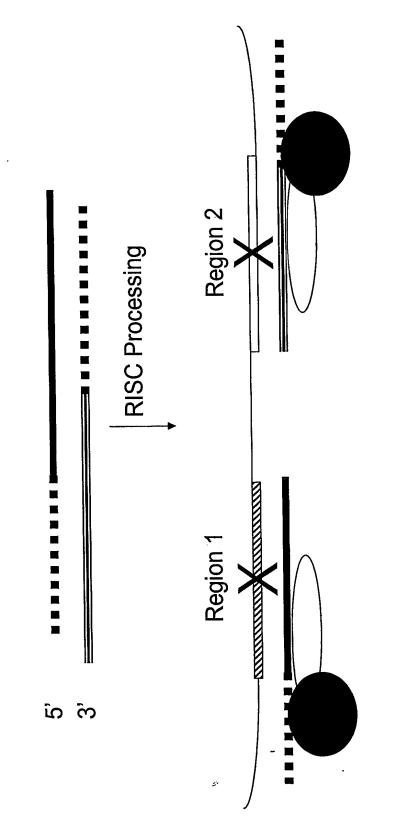


distinct complementary regions and a self complementary/palindrome region Figure 19: Examples of hairpin multifunctional siNA constructs with



Target 2 RNA Target 1 RNA Figure 20: Example of multifunctional siNA targeting two Separate Target nucleic acid sequences RISC Processing OR က်က် X = cleavage

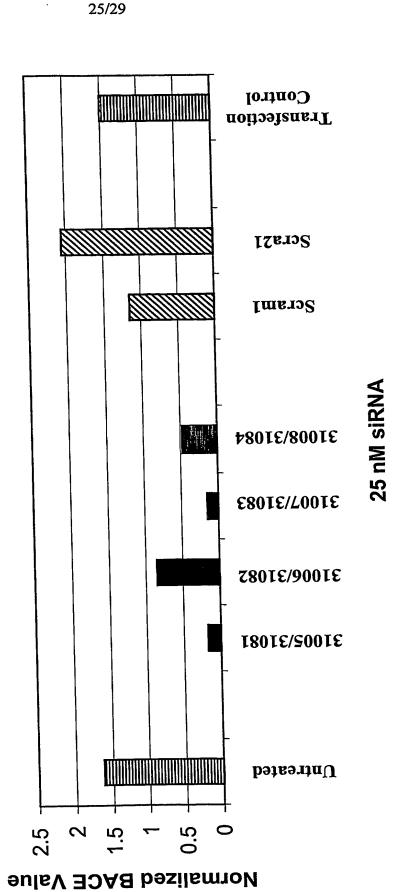
Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence



X = cleavage

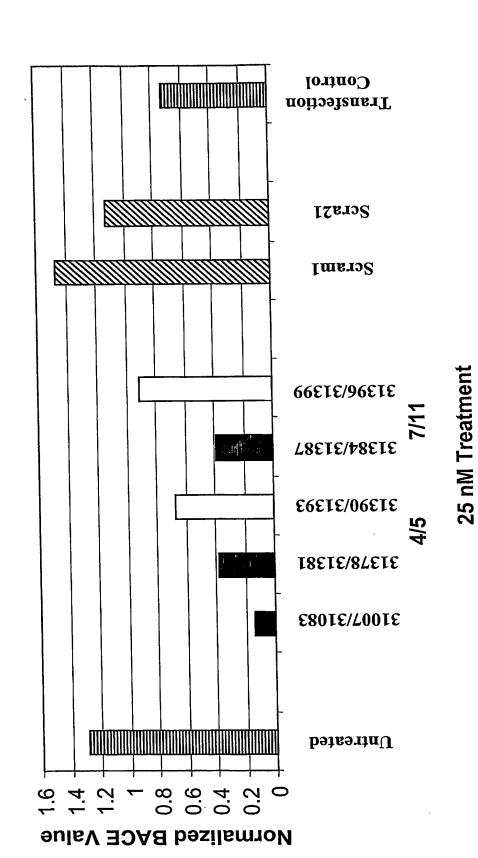
WO 2005/003350

Figure 22: A549 24h BACE mRNA Expression



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Figure 23: A549 24h BACE mRNA Expression using modified siNA



WO 2005/003350 PCT/US2004/020516

FIGURE 24

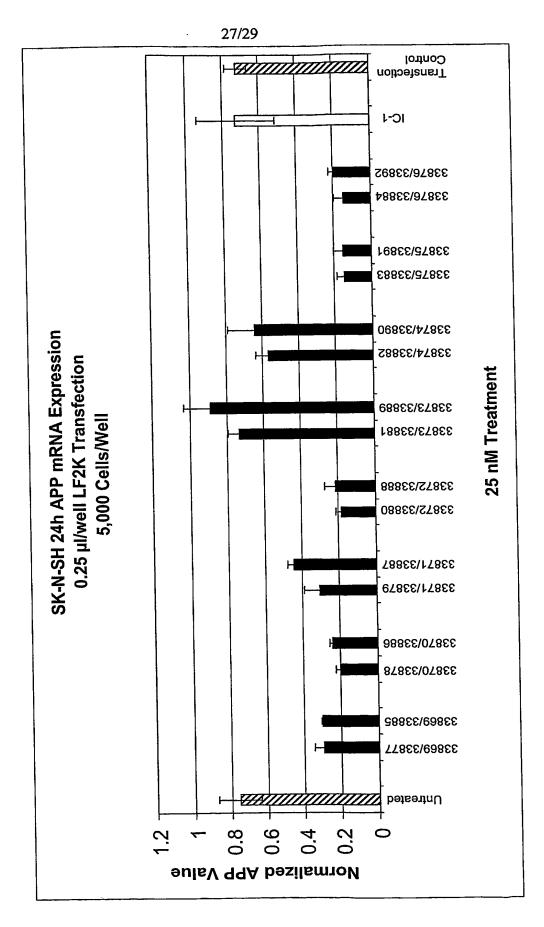
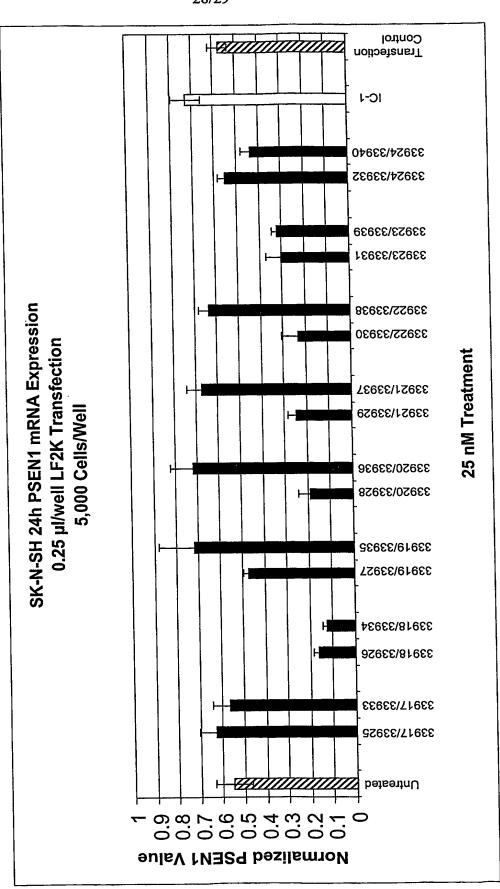


FIGURE 25



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FIGURE 26

